REMARKS

Upon entry of this amendment, claims 18-22, 27-29, 31-32 and 35-36 are pending in the instant application. Claims 23-26, 30, 33 and 34 have been cancelled herein without prejudice or disclaimer, and Applicant reserves the right to prosecute that subject matter, as well as the originally presented claims, in continuing applications. Claims 18-22, 27-29 and 31-32 have been amended, and claims 35-36 have been added. Support for the claim amendments presented herein can be found throughout the specification and in the claims as originally filed. For example, support for the isolated nucleic acids recited by new claims 35-36 is found at least at page 2, lines 21-23; at page 13, lines 29-35; and in Figure 8. Accordingly, no new matter has been added by these amendments.

1. Status of Application, Amendments and/or Claims

Applicants note that the substitute specification filed on May 15, 2002 (Paper No. 5) has been entered and that the amendments filed on September 26, 2001 (Paper No. 7) and May 15, 2002 (Paper No. 8) have been entered in full.

Applicants further note that claims 30, 33 and 34 have been cancelled herein, as being drawn to a nonelected invention. Applicant reserves the right to prosecute the cancelled subject matter in related applications.

2. Matter of Record

The Examiner has indicated that the substitute specification filed May 15, 2002 "improperly entered claims 72-88." (Office Action, page 2). The Examiner has renumbered the claims presented with the May 15, 2002 substitute specification as claims 1-17 under 37 C.F.R. 1.126. According to the Examiner, the Examiner has cancelled claims 1-17 and renumbered claims 72-88 as claims 18-34, because the September 26, 2001 Amendment requested the cancellation of all pending claims and the addition of new claims 72-88. Applicants note that the Amendment filed May 15, 2002, in conjunction with the substitute specification, further amended renumbered claims 18-34 (formerly claims 72-88). As the May 15, 2002 Amendment

has been entered in full (*see* Office Action, page 2, line 4), the listing of claims presented herein includes the amendments to renumbered claims 18-34 (formerly claims 72-88).

3. Claim Rejections Under 35 U.S.C. § 101

The Examiner has rejected claims 18-29, 31 and 32 under 35 U.S.C. § 101 for lack of utility. In particular, the Examiner has asserted that "the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility." (Office Action, page 3). According to the Examiner, the specification does not disclose any information regarding "true ligands or functional characteristics/mechanisms of action of SECX (clone 432429-2)." (Office Action, page 3). Applicants note that claims 23-26 have been cancelled herein. Thus, any rejection of these claims has been rendered moot and should be withdrawn. Applicants traverse this rejection to the extent it applies to pending claims 18-22, 27-29 and 31-32.

Applicants contend that the nucleic acids of the claimed invention have a specific, substantial and credible utility, and are, therefore, patentable under 35 U.S.C. § 101. Applicants assert that the SECX clone 4323229-2 (also referred to herein as CG52643-02) can be used, *inter alia*, in the detection and/or differentiation of various forms of cancer and in a variety of cancer-related diagnostic applications.

In support of these assertions, Applicants submit herewith a Declaration under 37 C.F.R. § 1.132, by Valerie Gerlach, Ph.D., an employee of CuraGen Corp., the assignee of the instant application. As noted by Dr. Gerlach, the SECX clone 4323229-2 nucleic acid and polypeptide can be used in therapeutic and diagnostic applications in cancers, such as, for example, kidney, lung, breast, bladder and/or ovarian cancers. (See Gerlach Declaration, ¶ 6-7).

Dr. Gerlach describes how the data presented in the Appendix of the Declaration depicts the scaled results of real time quantitative polymerase chain reaction-based gene expression analyses performed using a SECX clone 4323229-2 gene-specific primer-probe set to measure the relative SECX clone 4323229-2 expression levels in normal cells or tissues, and pathological tissue samples. The Ag2812 and Ag2822 primer sets used are found in Tables AA and AB of the Appendix. As shown in Tables AC – AE of the Appendix, the Relative Expression Score for

each sample indicates the relative quantity of a SECX clone 4323229-2 transcript, with 0.0 indicating no detectable expression and 100.0 indicating highest detectable expression level.

As described by Dr. Gerlach, the data presented in the Appendix of the Declaration demonstrates that expression of the 4324229-2 (CG52643-02) gene (SEQ ID NO: 15) was higher in normal kidney tissue compared to kidney tumors. Specifically, in one experiment, expression of this gene was downregulated in six out of nine kidney tumors, when compared to matched normal adjacent tissue. (See Gerlach Declaration, ¶ 6; Appendix Table AC). These results were confirmed in a second experiment which demonstrated that expression of the 4324229-2 gene was downregulated in eight out of eight kidney cancer samples, when compared to normal adjacent controls tissue. (See Gerlach Declaration, ¶ 6; Appendix Table AE). In contrast, expression of this gene was upregulated in six out of ten lung cancer cell lines relative to normal lung samples. (See Gerlach Declaration, ¶ 6; Appendix Table AD). Expression of the 4324229-2 gene was also upregulated in seven out of eight breast cancers compared to normal breast samples, including in two pairs of samples with tumor and matched normal adjacent tissue. (See Gerlach Declaration, ¶ 6; Appendix Table AE). Finally, expression of this gene was upregulated in two out of two bladder cancer samples and in one out of two ovarian cancer specimens. (See Gerlach Declaration, ¶ 6; Appendix Table AE). These results demonstrate that the SECX clone 4323229-2 nucleic acid and polypeptide can be used in therapeutic and diagnostic applications in cancers, including, for example, kidney, lung, breast, bladder and ovarian cancers.

Consistent with the teachings of the specification and the data presented in the attached Declaration and Exhibits, Applicants submit that it is clear that the nucleic acids of the present invention have credible, specific and substantial utilities. Accordingly, Applicants request that this rejection be withdrawn.

4. Claim Rejections Under 35 U.S.C. § 112, first paragraph

Claims 18-29, 31 and 32 have been rejected under 35 U.S.C. § 112, first paragraph. According to the Examiner, one of ordinary skill in the art "would not know how to use the claimed invention," because the nucleic acids of the claimed invention lack utility. (Office Action, page 5). For all of the reasons set forth above, the nucleic acids of the claimed invention

have credible, specific and substantial utilities and are, therefore, patentable under 35 U.S.C. § 101. Accordingly, this rejection under 35 U.S.C. § 112, first paragraph should be withdrawn.

Enablement

Claims 18-29, 31 and 32 have also been rejected under 35 U.S.C. § 112, first paragraph for lack of enablement. According to the Examiner, the instant specification "has not provided sufficient guidance as to how to make and use the encoded polypeptides which are not 100% identical to the polypeptide of SEQ ID NO: 16." (Office Action, page 5). Applicants note that claims 23-26 have been cancelled herein. Thus, any rejection of these claims has been rendered moot and should be withdrawn. Applicants traverse this rejection to the extent it applies to pending claims 18-22, 27-29 and 31-32.

Applicants note that claim 18 has been amended herein to recite isolated nucleic acids comprising a nucleic acid sequence encoding a polypeptide of SEQ ID NO: 16 or a nucleic acid sequence that is at least 90% identical to the nucleic acid encoding a polypeptide of SEQ ID NO: 16. In addition, claims 20-22 have been amended herein to delete all references to complements, mutants and/or variants of the nucleic acids of claim 18. Thus, the pending claims are not directed to *any* mutant, variant and/or fragment of a nucleic acid sequence encoding a polypeptide of SEQ ID NO: 16. Rather, these claims are directed to a nucleic acid encoding a polypeptide of SEQ ID NO: 16, or a specific subset of nucleic acids that are at least 90% identical to the nucleic acid encoding a polypeptide of SEQ ID NO: 16. Contrary to the Examiner's assertion, Applicants contend that one of ordinary skill in the art could identify and prepare nucleic acids that are 90% identical to the nucleic acid encoding a polypeptide of SEQ ID NO: 16 with routine experimentation using standard techniques known to those skilled in the art. For example, the instant specification discloses the use of computer programs known in the art to determine homology between nucleic acid sequences. (See specification at page 33, line 26 through page 34, line 19). Accordingly, Applicants contend that claim 18, as amended herein, is enabled by the specification. Therefore, Applicants request that the Examiner withdraw this rejection.

Written Description

The Examiner has also rejected claims 18-29, 31 and 32 under 35 U.S.C. § 112, first paragraph for lack of written description. According to the Examiner, the specification "provides adequate written description for SEQ ID Nos 15 and 16, but not variants." (Office Action, page 7). Again, Applicants note that claims 23-26 have been cancelled herein. Thus, any rejection of these claims has been rendered moot and should be withdrawn. Applicants traverse this rejection to the extent it applies to pending claims 18-22, 27-29 and 31-32.

As described above, the pending claims have been amended herein to remove all references to complements, mutants and/or variants of the nucleic acid sequences presented in Figures 1-13 and 18-19 of the instant specification. In addition, as noted, claim 18 has been amended to recite isolated nucleic acids comprising a nucleic acid sequence encoding a polypeptide of SEQ ID NO: 16 or a nucleic acid sequence that is at least 90% identical to the nucleic acid encoding a polypeptide of SEQ ID NO: 16. Such nucleic acids are disclosed throughout the specification as-filed. For example, the specification discloses at page 21, line 27 through page 22, line 16 that the nucleic acids of the claimed invention include derivatives and analogs that are at least 80%-95% identical to the nucleotide sequences shown in Figures 1-13 and 18-19 of the instant specification. Accordingly, Applicants contend that the pending claims are fully described by the as-filed specification. Therefore, this rejection should be withdrawn.

5. Claim Rejections Under 35 U.S.C. § 112, second paragraph

The Examiner has rejected claims 20, 21, 24 and 25 under 35 U.S.C. § 112, second paragraph as being indefinite.

With regard to claims 20 and 21, the Examiner has asserted that these claims are directed to nucleic acids that encode a polypeptide "or its complement." Applicants traverse this rejection. Claims 20-21 have been amended to remove all reference to the term "complement." Accordingly, this rejection should be withdrawn.

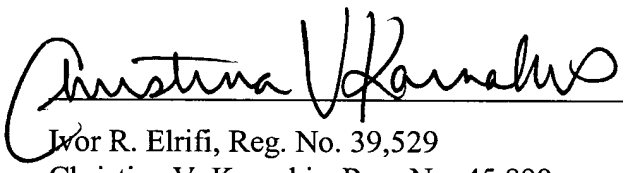
With regard to claims 24-25, the Examiner has asserted that "stringency is relative, and the art does not recognize a single set of conditions as stringent." Applicants note that claims 24-

25 have been cancelled herein. Thus, any rejection of these claims has been rendered moot and should be withdrawn.

CONCLUSION

On the basis of the foregoing amendments, Applicants respectfully submit that the pending claims are in condition for allowance. If there are any questions regarding these amendments and remarks, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,



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APPENDIX

Quantitative expression analysis of 4324229-2 (CG52643-02) in various cells and tissues

The quantitative expression of 4324229-2 was assessed using microtiter plates containing RNA samples from a variety of normal and pathology-derived cells, cell lines and tissues using real time quantitative PCR (RTQ-PCR) performed on an Applied Biosystems (Foster City, CA) ABI PRISM® 7700 or an ABI PRISM® 7900 HT Sequence Detection System.

RNA integrity of all samples was determined by visual assessment of agarose gel electropherograms using 28S and 18S ribosomal RNA staining intensity ratio as a guide (2:1 to 2.5:1 28s:18s) and the absence of low molecular weight RNAs (degradation products). Control samples to detect genomic DNA contamination included RTQ-PCR reactions run in the absence of reverse transcriptase using probe and primer sets designed to amplify across the span of a single exon.

RNA samples were normalized in reference to nucleic acids encoding constitutively expressed genes (i.e., β-actin and GAPDH). Alternatively, non-normalized RNA samples were converted to single strand cDNA (sscDNA) using Superscript II (Invitrogen Corporation, Carlsbad, CA, Catalog No. 18064-147) and random hexamers according to the manufacturer's instructions. Reactions containing up to 10 μg of total RNA in a volume of 20 μl or were scaled up to contain 50 μg of total RNA in a volume of 100 μl and were incubated for 60 minutes at 42°C. sscDNA samples were then normalized in reference to nucleic acids as described above.

Probes and primers were designed according to Applied Biosystems *Primer Express* Software package (version I for Apple Computer's Macintosh Power PC) or a similar algorithm using the target sequence as input. Default reaction condition settings and the following parameters were set before selecting primers: 250 nM primer concentration; 58°-60° C primer melting temperature (Tm) range; 59° C primer optimal Tm; 2° C maximum primer difference (if probe does not have 5' G, probe Tm must be 10° C greater than primer Tm; and 75 bp to 100 bp amplicon size. The selected probes and primers were synthesized by Synthegen (Houston, TX). Probes were double purified by HPLC to remove uncoupled dye and evaluated by mass spectroscopy to verify coupling of reporter and quencher dyes to the 5' and 3' ends of the probe, respectively. Their final concentrations were: 900 nM forward and reverse primers, and 200nM probe.

Normalized RNA was spotted in individual wells of a 96 or 384-well PCR plate (Applied Biosystems, Foster City, CA). PCR cocktails included a single gene-specific probe and primers set or two multiplexed probe and primers sets. PCR reactions were done using TaqMan® One-Step RT-PCR Master Mix (Applied Biosystems, Catalog No. 4313803) following manufacturer's instructions. Reverse transcription was performed at 48° C for 30 minutes followed by amplification/PCR cycles: 95° C 10 min, then 40 cycles at 95° C for 15 seconds, followed by 60° C for 1 minute. Results were recorded as CT values (cycle at which a given sample crosses a threshold level of fluorescence) and plotted using a log scale, with the difference in RNA concentration between a given sample and the sample with the lowest CT value being represented as 2 to the power of delta CT. The

percent relative expression was the reciprocal of the RNA difference multiplied by 100. CT values below 28 indicate high expression, between 28 and 32 indicate moderate expression, between 32 and 35 indicate low expression and above 35 reflect levels of expression that were too low to be measured reliably.

Normalized sscDNA was analyzed by RTQ-PCR using 1X TaqMan® Universal Master mix (Applied Biosystems; catalog No. 4324020), following the manufacturer's instructions. PCR amplification and analysis were done as described above.

Panels 1, 1.1, 1.2, and 1.3D

Panels 1, 1.1, 1.2 and 1.3D included 2 control wells (genomic DNA control and chemistry control) and 94 wells of cDNA samples from cultured cell lines and primary normal tissues. Cell lines were derived from carcinomas (ca) including: lung, small cell (s cell var), non small cell (non-s or non-sm); breast; melanoma; colon; prostate; glioma (glio), astrocytoma (astro) and neuroblastoma (neuro); squamous cell (squam); ovarian; liver; renal; gastric and pancreatic from the American Type Culture Collection (ATCC, Bethesda, MD). Normal tissues were obtained from individual adults or fetuses and included: adult and fetal skeletal muscle, adult and fetal heart, adult and fetal kidney, adult and fetal liver, adult and fetal lung, brain, spleen, bone marrow, lymph node, pancreas, salivary gland, pituitary gland, adrenal gland, spinal cord, thymus, stomach, small intestine, colon, bladder, trachea, breast, ovary, uterus, placenta, prostate, testis and adipose. The following abbreviations are used in reporting the results: metastasis (met); pleural effusion (pl. eff or pl effusion) and * indicates established from metastasis.

General_screening_panel_v1.4, v1.5, v1.6 and v1.7

Panels 1.4, 1.5, 1.6 and 1.7 were as described for Panels 1, 1.1, 1.2 and 1.3D, above except that normal tissue samples were pooled from 2 to 5 different adults or fetuses.

Panels 2D, 2.2, 2.3 and 2.4

Panels 2D, 2.2, 2.3 and 2.4 included 2 control wells and 94 wells containing RNA or cDNA from human surgical specimens procured through the National Cancer Institute's Cooperative Human Tissue Network (CHTN) or the National Disease Research Initiative (NDRI), Ardais (Lexington, MA) or Clinomics BioSciences (Frederick, MD). Tissues included human malignancies and in some cases matched adjacent normal tissue (NAT). Information regarding histopathological assessment of tumor differentiation grade as well as the clinical stage of the patient from which samples were obtained was generally available. Normal tissue RNA and cDNA samples were purchased from various commercial sources such as Clontech (Palo Alto, CA), Research Genetics and Invitrogen (Carlsbad, CA).

HASS Panel v 1.0

The HASS Panel v1.0 included 93 cDNA samples and two controls including: 81 samples of cultured human cancer cell lines subjected to serum starvation, acidosis and anoxia according to established procedures for various lengths of time; 3 human primary cells; 9 malignant brain cancers (4 medulloblastomas and 5 glioblastomas); and 2

controls. Cancer cell lines (ATCC) were cultured using recommended conditions and included: breast, prostate, bladder, pancreatic and CNS. Primary human cells were obtained from Clonetics (Walkersville, MD). Malignant brain samples were gifts from the Henry Ford Cancer Center.

ARDAIS Panel v1.0 and v1.1

The ARDAIS Panel v1.0 and v1.1 included 2 controls and 22 test samples including: human lung adenocarcinomas, lung squamous cell carcinomas, and in some cases matched adjacent normal tissues (NAT) obtained from Ardais (Lexington, MA). Unmatched malignant and non-malignant RNA samples from lungs with gross histopathological assessment of tumor differentiation grade and stage and clinical state of the patient were obtained from Ardais.

ARDAIS Prostate v1.0

ARDAIS Prostate v1.0 panel included 2 controls and 68 test samples of human prostate malignancies and in some cases matched adjacent normal tissues (NAT) obtained from Ardais (Lexington, MA). RNA from unmatched malignant and non-malignant prostate samples with gross histopathological assessment of tumor differentiation grade and stage and clinical state of the patient were also obtained from Ardais.

ARDAIS Kidney v1.0

ARDAIS Kidney v1.0 panel included 2 control wells and 44 test samples of human renal cell carcinoma and in some cases matched adjacent normal tissue (NAT) obtained from Ardais (Lexington, MA). RNA from unmatched renal cell carcinoma and normal tissue with gross histopathological assessment of tumor differentiation grade and stage and clinical state of the patient were also obtained from Ardais.

ARDAIS Breast v1.0

ARDAIS Breast v1.0 panel included 2 control wells and 71 test samples of human breast malignancies and in some cases matched adjacent normal tissue (NAT) obtained from Ardais (Lexington, MA). RNA from unmatched malignant and non-malignant breast samples with gross histopathological assessment of tumor differentiation grade and stage and clinical state of the patient were also obtained from Ardais.

Panel 3D, 3.1 and 3.2

Panels 3D, 3.1, and 3.2 included two controls, 92 cDNA samples of cultured human cancer cell lines and 2 samples of human primary cerebellum. Cell lines (ATCC, National Cancer Institute (NCI), German tumor cell bank) were cultured as recommended and were derived from: squamous cell carcinoma of the tongue, melanoma, sarcoma, leukemia, lymphoma, and epidermoid, bladder, pancreas, kidney, breast, prostate, ovary, uterus, cervix, stomach, colon, lung and CNS carcinomas.

Panels 4D, 4R, and 4.1D

Panels 4D, 4R, and 4.1D included 2 control wells and 94 test samples of RNA (Panel 4R) or cDNA (Panels 4D and 4.1D) from human cell lines or tissues related to inflammatory conditions. Controls included total RNA from normal tissues such as colon, lung (Stratagene, La Jolla, CA), thymus and kidney (Clontech, Palo Alto, CA). Total RNA from cirrhotic and lupus kidney was obtained from BioChain Institute, Inc., (Hayward, CA). Crohn's intestinal and ulcerative colitis samples were obtained from the National Disease Research Interchange (NDRI, Philadelphia, PA). Cells purchased from Clonetics (Walkersville, MD) included: astrocytes, lung fibroblasts, dermal fibroblasts, coronary artery smooth muscle cells, small airway epithelium, bronchial epithelium, microvascular dermal endothelial cells, microvascular lung endothelial cells, human pulmonary aortic endothelial cells, and human umbilical vein endothelial. These primary cell types were activated by incubating with various cytokines (IL-1 beta ~1-5 ng/ml, TNF alpha ~5-10 ng/ml, IFN gamma ~20-50 ng/ml, IL-4 ~5-10 ng/ml, IL-9 ~5-10 ng/ml, IL-13 5-10 ng/ml) or combinations of cytokines as indicated. Starved endothelial cells were cultured in the basal media (Clonetics, Walkersville, MD) with 0.1% serum.

Mononuclear cells were prepared from blood donations using Ficoll. LAK cells were cultured in culture media [DMEM, 5% FCS (Hyclone, Logan, UT), 100 mM non essential amino acids (Gibco/Life Technologies, Rockville, MD), 1 mM sodium pyruvate (Gibco), mercaptoethanol 5.5 x 10^{-5} M (Gibco), and 10 mM Hepes (Gibco)] and interleukin 2 for 4-6 days. Cells were activated with 10-20 ng/ml PMA and 1-2 μg/ml ionomycin, 5-10 ng/ml IL-12, 20-50 ng/ml IFN gamma or 5-10 ng/ml IL-18 for 6 hours. In some cases, mononuclear cells were cultured for 4-5 days in culture media with ~5 mg/ml PHA (phytohemagglutinin) or PWM (pokeweed mitogen; Sigma-Aldrich Corp., St. Louis, MO). Samples were taken at 24, 48 and 72 hours for RNA preparation. MLR (mixed lymphocyte reaction) samples were obtained by taking blood from two donors, isolating the mononuclear cells using Ficoll and mixing them 1:1 at a final concentration of ~$2x10^6$ cells/ml in culture media. The MLR samples were taken at various time points from 1-7 days for RNA preparation.

Monocytes were isolated from mononuclear cells using CD14 Miltenyi Beads, +ve VS selection columns and a Vario Magnet (Miltenyi Biotec, Auburn, CA) according to the manufacturer's instructions. Monocytes were differentiated into dendritic cells by culturing in culture media with 50 ng/ml GMCSF and 5 ng/ml IL-4 for 5-7 days. Macrophages were prepared by culturing monocytes for 5-7 days in culture media with ~50 ng/ml 10% type AB Human Serum (Life technologies, Rockville, MD) or MCSF (Macrophage colony stimulating factor; R&D, Minneapolis, MN). Monocytes, macrophages and dendritic cells were stimulated for 6 or 12-14 hours with 100 ng/ml lipopolysaccharide (LPS). Dendritic cells were also stimulated with 10 μg/ml anti-CD40 monoclonal antibody (Pharmingen, San Diego, CA) for 6 or 12-14 hours.

CD4+ lymphocytes, CD8+ lymphocytes and NK cells were also isolated from mononuclear cells using CD4, CD8 and CD56 Miltenyi beads, positive VS selection columns and a Vario Magnet (Miltenyi Biotec, Auburn, CA) according to the manufacturer's instructions. CD45+RA and CD45+RO CD4+ lymphocytes were isolated

by depleting mononuclear cells of CD8+, CD56+, CD14+ and CD19+ cells using CD8, CD56, CD14 and CD19 Miltenyi beads and positive selection. CD45RO Miltenyi beads were then used to separate the CD45+RO CD4+ lymphocytes from CD45+RA CD4+ lymphocytes. CD45+RA CD4+, CD45+RO CD4 +and CD8+ lymphocytes were cultured in culture media at 10^6 cells/ml in culture plates precoated overnight with 0.5 mg/ml anti-CD28 (Pharmingen, San Diego, CA) and 3 μg/ml anti-CD3 (OKT3, ATCC) in PBS. After 6 and 24 hours, the cells were harvested for RNA preparation. To prepare chronically activated CD8+ lymphocytes, isolated CD8+ lymphocytes were activated for 4 days on anti-CD28, anti-CD3 coated plates and then harvested and expanded in culture media with IL-2 (1 ng/ml). These CD8+ cells were activated again with plate bound anti-CD3 and anti-CD28 for 4 days and expanded as described above. RNA was isolated 6 and 24 hours after the second activation and after 4 days of the second expansion culture. Isolated NK cells were cultured in culture media with 1 ng/ml IL-2 for 4-6 days before RNA was prepared.

B cells were prepared from minced and sieved tonsil tissue (NDRI). Tonsil cells were pelleted and resupended at 10^6 cells/ml in culture media. Cells were activated using 5 μg/ml PWM (Sigma-Aldrich Corp., St. Louis, MO) or ~10 μg/ml anti-CD40 (Pharmingen, San Diego, CA) and 5-10 ng/ml IL-4. Cells were harvested for RNA preparation after 24, 48 and 72 hours.

To prepare primary and secondary Th1/Th2 and Tr1 cells, umbilical cord blood CD4+ lymphocytes (Poietic Systems, German Town, MD) were cultured at 10^5-10^6cells/ml in culture media with IL-2 (4 ng/ml) in 6-well Falcon plates (precoated overnight with 10 μg/ml anti-CD28 (Pharmingen) and 2 μg/ml anti-CD3 (OKT3; ATCC) then washed twice with PBS).

To stimulate Th1 phenotype differentiation, IL-12 (5 ng/ml) and anti-IL4 (1 μg/ml) were used; for Th2 phenotype differentiation, IL-4 (5 ng/ml) and anti-IFN gamma (1 μg/ml) were used; and for Tr1 phenotype differentiation, IL-10 (5 ng/ml) was used. After 4-5 days, the activated Th1, Th2 and Tr1 lymphocytes were washed once with DMEM and expanded for 4-7 days in culture media with IL-2 (1 ng/ml). Activated Th1, Th2 and Tr1 lymphocytes were re-stimulated for 5 days with anti-CD28/CD3 and cytokines as described above with the addition of anti-CD95L (1 μg/ml) to prevent apoptosis. After 4-5 days, the Th1, Th2 and Tr1 lymphocytes were washed and expanded in culture media with IL-2 for 4-7 days. Activated Th1 and Th2 lymphocytes were maintained for a maximum of three cycles. RNA was prepared from primary and secondary Th1, Th2 and Tr1 after 6 and 24 hours following the second and third activations with plate-bound anti-CD3 and anti-CD28 mAbs and 4 days into the second and third expansion cultures.

Leukocyte cells lines Ramos, EOL-1, KU-812 were obtained from the ATCC. EOL-1 cells were further differentiated by culturing in culture media at 5 x10^5 cells/ml with 0.1 mM dbcAMP for 8 days, changing the media every 3 days and adjusting the cell concentration to 5 x10^5 cells/ml. RNA was prepared from resting cells or cells activated with PMA (10 ng/ml) and ionomycin (1 μg/ml) for 6 and 14 hours. RNA was prepared from resting CCD 1106 keratinocyte cell line (ATCC) or from cells activated with ~5 ng/ml TNF alpha and 1 ng/ml IL-1 beta. RNA was prepared from resting NCI-H292,

airway epithelial tumor cell line (ATCC) or from cells activated for 6 and 14 hours in culture media with 5 ng/ml IL-4, 5 ng/ml IL-9, 5 ng/ml IL-13, and 25 ng/ml IFN gamma.

RNA was prepared by lysing approximately 10^7 cells/ml using Trizol (Gibco BRL) then adding 1/10 volume of bromochloropropane (Molecular Research Corporation, Cincinnati, OH), vortexing, incubating for 10 minutes at room temperature and then spinning at 14,000 rpm in a Sorvall SS34 rotor. The aqueous phase was placed in a 15 ml Falcon Tube and an equal volume of isopropanol was added and left at –20° C overnight. The precipitated RNA was spun down at 9,000 rpm for 15 min and washed in 70% ethanol. The pellet was redissolved in 300 µl of RNAse-free water with 35 ml buffer (Promega, Madison, WI) 5 µl DTT, 7 µl RNAsin and 8 µl DNAse and incubated at 37° C for 30 minutes to remove contaminating genomic DNA, extracted once with phenol chloroform and re-precipitated with 1/10 volume of 3 M sodium acetate and 2 volumes of 100% ethanol. The RNA was spun down, placed in RNAse free water and stored at –80° C.

AI_comprehensive panel_v1.0

Autoimmunity (AI) comprehensive panel v1.0 included two controls and 89 cDNA test samples isolated from male (M) and female (F) surgical and postmortem human tissues that were obtained from the Backus Hospital and Clinomics (Frederick, MD). Tissue samples included : normal, adjacent (Adj); matched normal adjacent (match control); joint tissues (synovial (Syn) fluid, synovium, bone and cartilage, osteoarthritis (OA), rheumatoid arthritis (RA)); psoriatic; ulcerative colitis colon; Crohns disease colon; and emphysmatic, asthmatic, allergic and chronic obstructive pulmonary disease (COPD) lung.

Pulmonary and General inflammation (PGI) panel v1.0

Pulmonary and General inflammation (PGI) panel v1.0 included two controls and 39 test samples isolated as surgical or postmortem samples. Tissue samples include: five normal lung samples obtained from Maryland Brain and Tissue Bank, University of Maryland (Baltimore, MD), International Bioresource systems, IBS (Tuscon, AZ), and Asterand (Detroit, MI), five normal adjacent intestine tissues (NAT) from Ardais (Lexington, MA), ulcerative colitis samples (UC) from Ardais (Lexington, MA); Crohns disease colon from NDRI, National Disease Research Interchange (Philadelphia, PA); emphysematous tissue samples from Ardais (Lexington, MA) and Genomic Collaborative Inc. (Cambridge, MA), asthmatic tissue from Maryland Brain and Tissue Bank, University of Maryland (Baltimore, MD) and Genomic Collaborative Inc (Cambridge, MA) and fibrotic tissue from Ardais (Lexinton, MA) and Genomic Collaborative (Cambridge, MA).

AI.05 chondrosarcoma

AI.05 chondrosarcoma plates included SW1353 cells (ATCC) subjected to serum starvation and treated for 6 and 18 h with cytokines that are known to induce MMP (1, 3 and 13) synthesis (e.g. IL1beta). These treatments included: IL-1beta (10 ng/ml), IL-1beta + TNF-alpha (50 ng/ml), IL-1beta + Oncostatin (50 ng/ml) and PMA (100 ng/ml).

Supernatants were collected and analyzed for MMP 1, 3 and 13 production. RNA was prepared from these samples using standard procedures.

Panels 5D and 5I

Panel 5D and 5I included two controls and cDNAs isolated from human tissues, human pancreatic islets cells, cell lines, metabolic tissues obtained from patients enrolled in the Gestational Diabetes study (described below), and cells from different stages of adipocyte differentiation, including differentiated (AD), midway differentiated (AM), and undifferentiated (U; human mesenchymal stem cells).

Gestational Diabetes study subjects were young (18 - 40 years), otherwise healthy women with and without gestational diabetes undergoing routine (elective) Caesarean section. Uterine wall smooth muscle (UT), visceral (Vis) adipose, skeletal muscle (SK), placenta (Pl) greater omentum adipose (GO Adipose) and subcutaneous (SubQ) adipose samples (less than 1 cc) were collected, rinsed in sterile saline, blotted and flash frozen in liquid nitrogen. Patients included: Patient 2, an overweight diabetic Hispanic not on insulin; Patient 7-9, obese non-diabetic Caucasians with body mass index (BMI) greater than 30; Patient 10, an overweight diabetic Hispanic, on insulin; Patient 11, an overweight nondiabetic African American; and Patient 12, a diabetic Hispanic on insulin.

Differentiated adipocytes were obtained from induced donor progenitor cells (Clonetics, Walkersville, MD). Differentiated human mesenchymal stem cells (HuMSCs) were prepared as described in Mark F. Pittenger, et al., Multilineage Potential of Adult Human Mesenchymal Stem Cells *Science* Apr 2 1999: 143-147. mRNA was isolated and sscDNA was produced from Trizol lysates or frozen pellets. Human cell lines (ATCC, NCI or German tumor cell bank) included: kidney proximal convoluted tubule, uterine smooth muscle cells, small intestine, liver HepG2 cancer cells, heart primary stromal cells and adrenal cortical adenoma cells. Cells were cultured, RNA extracted and sscDNA was produced using standard procedures.

Panel 5I also contains pancreatic islets (Diabetes Research Institute at the University of Miami School of Medicine).

Human Metabolic RTQ-PCR Panel

Human Metabolic RTQ-PCR Panel included two controls (genomic DNA control and chemistry control) and 211 cDNAs isolated from human tissues and cell lines relevant to metabolic diseases. This panel identifies genes that play a role in the etiology and pathogenesis of obesity and/or diabetes. Metabolic tissues including placenta (Pl), uterine wall smooth muscle (Ut), visceral adipose, skeletal muscle (Sk) and subcutaneous (SubQ) adipose were obtained from the Gestational Diabetes study (described above). Included in the panel are: Patients 7 and 8, obese non-diabetic Caucasians; Patient 12 a diabetic Caucasian with unknown BMI, on insulin (treated); Patient 13, an overweight diabetic Caucasian, not on insulin (untreated); Patient 15, an obese, untreated, diabetic Caucasian; Patient 17 and 25, untreated diabetic Caucasians of normal weight; Patient 18, an obese, untreated, diabetic Hispanic; Patient 19, a non-diabetic Caucasian of normal weight; Patient 20, an overweight, treated diabetic Caucasian; Patient 21 and 23, overweight non-

diabetic Caucasians; Patient 22, a treated diabetic Caucasian of normal weight; Patient 23, an overweight non-diabetic Caucasian; and Patients 26 and 27, obese, treated, diabetic Caucasians.

Total RNA was isolated from metabolic tissues including: hypothalamus, liver, pancreas, pancreatic islets, small intestine, psoas muscle, diaphragm muscle, visceral (Vis) adipose, subcutaneous (SubQ) adipose and greater omentum (Go) from 12 Type II diabetic (Diab) patients and 12 non diabetic (Norm) at autopsy. Control diabetic and non-diabetic subjects were matched where possible for: age; sex, male (M); female (F); ethnicity, Caucasian (CC); Hispanic (HI); African American (AA); Asian (AS); and BMI, 20-25 (Low BM), 26-30 (Med BM) or overweight (Overwt), BMI greater than 30 (Hi BMI) (obese).

RNA was extracted and ss cDNA was produced from cell lines (ATCC) by standard methods.

CNS Panels

CNS Panels CNSD.01, CNS Neurodegeneration V1.0 and CNS Neurodegeneration V2.0 included two controls and 46 to 94 test cDNA samples isolated from postmortem human brain tissue obtained from the Harvard Brain Tissue Resource Center (McLean Hospital). Brains were removed from calvaria of donors between 4 and 24 hours after death, and frozen at -80° C in liquid nitrogen vapor.

Panel CNSD.01

Panel CNSD.01 included two specimens each from: Alzheimer's disease, Parkinson's disease, Huntington's disease, Progressive Supernuclear Palsy (PSP), Depression, and normal controls. Collected tissues included: cingulate gyrus (Cing Gyr), temporal pole (Temp Pole), globus palladus (Glob palladus), substantia nigra (Sub Nigra), primary motor strip (Brodman Area 4), parietal cortex (Brodman Area 7), prefrontal cortex (Brodman Area 9), and occipital cortex (Brodman area 17). Not all brain regions are represented in all cases.

Panel CNS Neurodegeneration V1.0

The CNS Neurodegeneration V1.0 panel included: six Alzheimer's disease (AD) brains and eight normals which included no dementia and no Alzheimer's like pathology (control) or no dementia but evidence of severe Alzheimer's like pathology (Control Path), specifically senile plaque load rated as level 3 on a scale of 0-3; 0 no evidence of plaques, 3 severe AD senile plaque load. Tissues collected included: hippocampus, temporal cortex (Brodman Area 21), parietal cortex (Brodman area 7), occipital cortex (Brodman area 17) superior temporal cortex (Sup Temporal Ctx) and inferior temporal cortex (Inf Temproal Ctx).

Gene expression was analyzed after normalization using a scaling factor calculated by subtracting the Well mean (CT average for the specific tissue) from the Grand mean (average CT value for all wells across all runs). The scaled CT value is the result of the raw CT value plus the scaling factor.

Panel CNS Neurodegeneration V2.0

The CNS Neurodegeneration V2.0 panel included sixteen cases of Alzheimer's disease (AD) and twenty-nine normal controls (no evidence of dementia prior to death) including fourteen controls (Control) with no dementia and no Alzheimer's like pathology and fifteen controls with no dementia but evidence of severe Alzheimer's like pathology (AH3), specifically senile plaque load rated as level 3 on a scale of 0-3; 0 no evidence of plaques, 3 severe AD senile plaque load. Tissues from the temporal cortex (Brodman Area 21) included the inferior and superior temporal cortex that was pooled from a given individual (Inf & Sup Temp Ctx Pool).

A. 4324229-2 (CG52643-02)

Expression of gene CG52643-02 was assessed using the primer-probe sets Ag2812, Ag2822, Ag861, Ag10, Ag010b and Ag550, described in Tables AA, AB, AC, AD, AE and AF. Results of the RTQ-PCR runs are shown in Tables AG, AH and AI.

Table AA. Probe Name Ag2812

Primers	Sequences	Length	Start Position
Forward	5'-ctgtactcgctttgtggttca-3'	21	3037
Probe	TET-5'-cactggtctccttgcaagtttcctag-3'-TAMRA	26	3059
Reverse	5'-aatcttggtagcagcgcatac-3'	21	3091

Table AB. Probe Name Ag2822

Primers	Sequences	Length	Start Position
Forward	5'-tcttcatccaggtcctgctt-3'	20	1023
Probe	TET-5'-cttcagcacatgctgagccagttcg-3'-TAMRA	25	998
Reverse	5'-ttcagggacttagatgcagatg-3'	22	954

Table AC. Ardais Kidney 1.0

Column A - Rel. Exp.(%) Ag2822, Run 408430930			
Tissue Name	A	Tissue Name	A
Kidney cancer(10A8)	16.7	Kidney cancer(10C6)	**100.0**
Kidney NAT(10A9)	11.7	Kidney cancer(10C9)	0.1
Kidney cancer(10AA)	6.4	Kidney cancer(10D1)	0.5
Kidney NAT(10AB)	14.8	Kidney cancer(10CA)	0.1
Kidney cancer(10AC)	0.1	Kidney cancer(10D2)	0.0
Kidney NAT(10AD)	10.4	Kidney cancer(10CB)	0.0
Kidney cancer(10B6)	39.2	Kidney cancer(10D4)	0.2
Kidney NAT(10B7)	24.5	Kidney cancer(10CD)	0.3
Kidney cancer(10B8)	0.0	Kidney cancer(10D5)	3.5
Kidney NAT(10B9)	34.4	Kidney cancer(10CE)	1.5
Kidney cancer(10BC)	0.4	Kidney cancer(10D6)	2.4

Kidney NAT(10BD)	9.9	Kidney cancer(10CF)	25.5
Kidney cancer(10BE)	23.5	Kidney cancer(10D8)	0.3
Kidney NAT(10BF)	17.9	Kidney cancer(10CC)	0.9
Kidney cancer(10C2)	0.8	Kidney cancer(10D3)	0.7
Kidney NAT(10C3)	8.2	Kidney NAT(10D9)	16.8
Kidney cancer(10C4)	0.3	Kidney NAT(10DB)	11.1
Kidney NAT(10C5)	18.8	Kidney NAT(10DC)	27.5
Kidney cancer(10B4)	88.3	Kidney NAT(10DD)	8.6
Kidney cancer(10C8)	0.1	Kidney NAT(10DE)	9.0
Kidney cancer(10D0)	0.3	Kidney NAT(10B1)	8.3
Kidney cancer(10C0)	0.0	Kidney NAT(10DA)	26.1

Table AD. Panel 1.3D

Column A - Rel. Exp.(%) Ag2812, Run 157453866			
Tissue Name	**A**	**Tissue Name**	**A**
Liver adenocarcinoma	8.9	Kidney (fetal)	1.6
Pancreas	1.1	Renal ca. 786-0	0.0
Pancreatic ca. CAPAN 2	0.0	Renal ca. A498	0.9
Adrenal gland	4.9	Renal ca. RXF 393	0.0
Thyroid	0.6	Renal ca. ACHN	0.0
Salivary gland	0.1	Renal ca. UO-31	0.2
Pituitary gland	10.2	Renal ca. TK-10	0.0
Brain (fetal)	1.3	Liver	0.0
Brain (whole)	27.7	Liver (fetal)	0.0
Brain (amygdala)	22.7	Liver ca. (hepatoblast) HepG2	9.2
Brain (cerebellum)	14.5	Lung	1.7
Brain (hippocampus)	**100.0**	Lung (fetal)	0.2
Brain (substantia nigra)	2.4	Lung ca. (small cell) LX-1	5.4
Brain (thalamus)	39.5	Lung ca. (small cell) NCI-H69	29.9
Cerebral Cortex	97.9	Lung ca. (s.cell var.) SHP-77	13.0
Spinal cord	1.1	Lung ca. (large cell)NCI-H460	63.7
glio/astro U87-MG	1.5	Lung ca. (non-sm. cell) A549	25.7
glio/astro U-118-MG	0.7	Lung ca. (non-s.cell) NCI-H23	0.3
astrocytoma SW1783	0.0	Lung ca. (non-s.cell) HOP-62	0.0
neuro*; met SK-N-AS	1.2	Lung ca. (non-s.cl) NCI-H522	0.0
astrocytoma SF-539	0.0	Lung ca. (squam.) SW 900	1.2
astrocytoma SNB-75	1.3	Lung ca. (squam.) NCI-H596	13.1
glioma SNB-19	0.1	Mammary gland	0.4

glioma U251	0.0	Breast ca.* (pl.ef) MCF-7	2.3
glioma SF-295	0.0	Breast ca.* (pl.ef) MDA-MB-231	0.0
Heart (Fetal)	0.1	Breast ca.* (pl. ef) T47D	0.5
Heart	0.0	Breast ca. BT-549	0.0
Skeletal muscle (Fetal)	2.6	Breast ca. MDA-N	0.0
Skeletal muscle	0.0	Ovary	0.3
Bone marrow	0.0	Ovarian ca. OVCAR-3	0.0
Thymus	0.1	Ovarian ca. OVCAR-4	0.0
Spleen	0.0	Ovarian ca. OVCAR-5	6.3
Lymph node	0.3	Ovarian ca. OVCAR-8	0.3
Colorectal	0.2	Ovarian ca. IGROV-1	1.3
Stomach	0.3	Ovarian ca. (ascites) SK-OV-3	0.3
Small intestine	0.1	Uterus	0.0
Colon ca. SW480	0.6	Placenta	0.8
Colon ca.* SW620 (SW480 met)	5.8	Prostate	3.3
Colon ca. HT29	0.0	Prostate ca.* (bone met) PC-3	0.0
Colon ca. HCT-116	0.6	Testis	6.4
Colon ca. CaCo-2	0.4	Melanoma Hs688(A).T	0.0
CC Well to Mod Diff (ODO3866)	0.0	Melanoma* (met) Hs688(B).T	0.1
Colon ca. HCC-2998	0.2	Melanoma UACC-62	0.0
Gastric ca. (liver met) NCI-N87	0.1	Melanoma M14	0.1
Bladder	0.2	Melanoma LOX IMVI	0.0
Trachea	2.1	Melanoma* (met) SK-MEL-5	1.0
Kidney	3.9	Adipose	0.0

Table AE. Panel 2D

Column A - Rel. Exp.(%) Ag2812, Run 157457938			
Tissue Name	**A**	**Tissue Name**	**A**
Normal Colon	4.6	Kidney Margin 8120608	5.6
CC Well to Mod Diff (ODO3866)	0.0	Kidney Cancer 8120613	0.4
CC Margin (ODO3866)	0.4	Kidney Margin 8120614	23.7
CC Gr.2 rectosigmoid (ODO3868)	0.8	Kidney Cancer 9010320	1.5
CC Margin (ODO3868)	0.8	Kidney Margin 9010321	25.9
CC Mod Diff (ODO3920)	0.4	Normal Uterus	0.0
CC Margin (ODO3920)	0.4	Uterine Cancer 064011	1.4
CC Gr.2 ascend colon (ODO3921)	0.0	Normal Thyroid	0.8
CC Margin (ODO3921)	0.3	Thyroid Cancer	0.7
CC from Partial Hepatectomy (ODO4309) Mets	3.1	Thyroid Cancer A302152	2.6

Liver Margin (ODO4309)	0.4	Thyroid Margin A302153	0.8
Colon mets to lung (OD04451-01)	1.5	Normal Breast	1.8
Lung Margin (OD04451-02)	2.6	Breast Cancer	6.6
Normal Prostate 6546-1	4.0	Breast Cancer (OD04590-01)	10.7
Prostate Cancer (OD04410)	1.9	Breast Cancer Mets (OD04590-03)	1.3
Prostate Margin (OD04410)	1.4	Breast Cancer Metastasis	33.0
Prostate Cancer (OD04720-01)	13.1	Breast Cancer	9.9
Prostate Margin (OD04720-02)	13.1	Breast Cancer	**100.0**
Normal Lung	14.3	Breast Cancer 9100266	8.0
Lung Met to Muscle (ODO4286)	1.3	Breast Margin 9100265	1.4
Muscle Margin (ODO4286)	27.5	Breast Cancer A209073	16.2
Lung Malignant Cancer (OD03126)	50.3	Breast Margin A209073	2.9
Lung Margin (OD03126)	18.7	Normal Liver	0.4
Lung Cancer (OD04404)	13.1	Liver Cancer	1.0
Lung Margin (OD04404)	4.3	Liver Cancer 1025	0.0
Lung Cancer (OD04565)	3.2	Liver Cancer 1026	2.2
Lung Margin (OD04565)	6.2	Liver Cancer 6004-T	1.1
Lung Cancer (OD04237-01)	7.0	Liver Tissue 6004-N	2.4
Lung Margin (OD04237-02)	3.2	Liver Cancer 6005-T	3.3
Ocular Mel Met to Liver (ODO4310)	3.4	Liver Tissue 6005-N	0.0
Liver Margin (ODO4310)	0.4	Normal Bladder	5.7
Melanoma Metastasis	8.5	Bladder Cancer	0.0
Lung Margin (OD04321)	9.5	Bladder Cancer	32.8
Normal Kidney	23.2	Bladder Cancer (OD04718-01)	1.4
Kidney Ca, Nuclear grade 2 (OD04338)	2.0	Bladder Normal Adjacent (OD04718-03)	0.0
Kidney Margin (OD04338)	21.5	Normal Ovary	0.9
Kidney Ca Nuclear grade 1/2 (OD04339)	4.2	Ovarian Cancer	11.7
Kidney Margin (OD04339)	28.9	Ovarian Cancer (OD04768-07)	0.6
Kidney Ca, Clear cell type (OD04340)	4.2	Ovary Margin (OD04768-08)	0.0
Kidney Margin (OD04340)	24.7	Normal Stomach	0.5
Kidney Ca, Nuclear grade 3 (OD04348)	0.4	Gastric Cancer 9060358	0.0
Kidney Margin (OD04348)	12.6	Stomach Margin 9060359	1.4
Kidney Cancer (OD04622-01)	1.4	Gastric Cancer 9060395	0.0
Kidney Margin (OD04622-03)	4.1	Stomach Margin 9060394	0.8
Kidney Cancer (OD04450-01)	0.0	Gastric Cancer 9060397	0.8
Kidney Margin (OD04450-03)	15.4	Stomach Margin 9060396	1.6
Kidney Cancer 8120607	0.0	Gastric Cancer 064005	0.0

Ardais Kidney 1.0 Summary: Ag2822 In general, expression of this gene was higher in normal kidney tissue compared to kidney tumors. Specifically, expression of this gene was downregulated in 6/9 kidney tumors when compared with their matched normal adjacent tissue. The lung cancer samples (N=30) had an average CT of 32, whereas the normal kidney samples (N=14) had an average CT of 28. These results are consistent with what was observed in Panel 2D. Differential gene expression is therefore useful in differentiating kidney tumor specimens from normal kidney tissue. Therapeutic stimulation of the activity of this gene or its protein product using nucleic acid, protein, antibody, or small molecule drugs is beneficial in the treatment of kidney cancer.

Panel 1.3D Summary: Ag2812 Expression of the CG52643-02 gene was highest in hippocampus (CT=28.3). This gene was also expressed at moderate levels in amygdala, substantia nigra, thalamus, cerebellum, and cerebral cortex. Therapeutic modulation of the activity of this gene or its protein product is useful in the treatment of central nervous system disorders such as Alzheimer's disease, Parkinson's disease, epilepsy, multiple sclerosis, schizophrenia and depression.

Expression of this gene was upregulated in 6 out of 10 lung cancer cell lines relative to normal lung. Gene or protein expression levels are useful for the differentiation and therefore detection of lung cancer. Therapeutic modulation of the activity of this gene or its protein product using nucleic acid, protein, antibody or small molecule drugs is useful in the treatment of lung cancer.

Panel 2D Summary: Ag2812 Expression of the CG52643-02 gene was highest in a breast cancer sample (CT=30.1). Expression of this gene was upregulated in 7 out of 8 breast cancers compared to normal breast, including in two pairs of samples with tumor and matched normal adjacent tissue. Furthermore, the CG52643-02 gene was overexpressed in additional breast cancer samples compared to normal breast by microarray analysis (data not shown). Expression of this gene was also upregulated in 2/2 bladder cancers and 1/2 ovarian cancer. Therefore, CG52643-02 gene or protein expression levels are useful in the differentiation of normal verses cancerous tissues and the diagnosis of breast, bladder and ovarian cancer. Therapeutic inhibition of the activity of this gene or its protein product using nucleic acid, protein, antibody, or small molecule drugs is beneficial in the treatment of breast, bladder, and ovarian cancer.

Expression of the CG52643-02 gene was downregulated in 8/8 kidney cancer samples when compared to their appropriate normal adjacent controls. Therapeutic stimulation of the activity of this gene or its protein product using nucleic acid, protein, antibody, or small molecule drugs is beneficial in the treatment of kidney cancer.